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Review

SHIFT WORK AND CANCER: STATE OF SCIENCE AND PRACTICAL CONSEQUENCES*

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In 2007, an expert Working Group convened by the IARC Monographs Programme concluded that shift work that involves circadian disruption is probably carcinogenic to humans (Group 2A). We scrutinised the epidemiological basis for this conclusion, with a focus on, but not limited to, breast and prostate cancers. We further considered practical consequences for shift workers in our industry against the background of new findings.

We carried out a literature search including the epidemiological studies cited by IARC and newer available literature on shift work and cancer.

Since the IARC assessment, eleven new studies have emerged, ten of which have already been published, with inconclusive results. Heterogeneity of exposure metrics and study outcomes and emphasis on positive but non-significant results make it difficult to draw general conclusions. Also, several reviews and commentaries, which have been published meanwhile, came to equivocal results. Published evidence is widely seen as suggestive but inconclusive for an adverse association between night work and breast cancer, and limited and inconsistent for cancers at other sites and all cancers combined.

At this point in time it can not be ruled out that shift work including night work may increase the risk for some cancers in those who perform it. However, shift schedules can be organised in ways that minimise the associated health risks, and the risks may be further reduced through the implementation of structured and sustained health promotion programs specifically tailored to the needs of shift workers.

KEY WORDS: *breast cancer, circadian disruption, night work, prostate cancer*

Nearly 20 % of the working population in Europe and North America works in shifts and because of the nature of the production processes involved - the chemical industry is particularly dependent on this type of work organisation. In 2007, an expert Working Group convened by the International Agency for the Research on Cancer (IARC) Monographs Programme concluded on the basis of "limited evidence in humans for the carcinogenicity of shift work that involves night work", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)" that shift work that involves circadian disruption is probably carcinogenic to humans (Group 2A) (1). This ruling, which was only published as a short "policy watch" notice, was soon challenged by other scientists on the basis of a systematic review of the relevant literature (2). However, an in-depth discussion of the IARC assessment has only recently become possible due to the fact that the full monograph was only published three years after the first communication (3). In this article we will shortly summarise the epidemiological basis for the IARC assessment and address some

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inconsistencies, which in our opinion had been given too little weight by IARC. We will then summarise the new literature on this topic and finally, based on practical experience from a major chemical company in Germany, address the question of consequences for the shift work organisation in industry. For the purpose of this article, shift work is always considered as work involving night work.

THE IARC ASSESSMENT

The IARC ruling was mainly based on two types of study populations; first, the published cancer experience from nurse cohort members with and without shift work, and second, the respective findings in flight attendants and pilots. In the latter case, long-haul flights across time zones were taken as a proxy for shift work, because they were considered to cause "circadian disruption", a concept which IARC sees as instrumental for the development of cancer in so exposed persons. Noteworthy, on the 200 pages of the monograph the term "circadian disruption" occurs approximately 40 times, with no definition provided. For the purpose of the following discussion we may tentatively assume that it refers to desynchronisation of two or more of the more than hundred known physiological processes, which show circadian periodicity in humans. However, IARC leaves open the question of which ones may be of relevance, and to which degree such a disruption would have to occur to be of biological significance.

As a matter of fact, most of IARC's ruling is thus based on the reports of female breast cancer. In evaluating the evidence in humans, IARC offers a very straight-forward approach: six out of eight studies (excluding female flight attendants) included in the review have shown modestly elevated risks, and the incidence of breast cancer was also modestly increased in most cohorts of female flight attendants (1). The following Table 1 with the main results from the eight studies in "non-aircraft" populations shows that this simplified comparison may not represent the full picture.

Elevated breast cancer risks appear either after having worked in shifts for 30 years (4, 9), or after a cumulative exposure to shift work of only six months (8). They also appear after having worked in shifts for a little more than three years, but only in women aged 50 years or more (7). Thus, even in this small subset of studies there is considerable heterogeneity regarding dose metrics and dose-response relations.

IARC scrutinised nine studies on breast cancer in aircraft crew (12-20). Most risk estimates from these studies are in the range between 1 and 2, but only four out of the nine studies reach at least borderline statistical significance (12, 14, 16, 18). IARC acknowledges the fact that aircraft crew is exposed to other possible carcinogenic agents, most notably cosmic radiation. Indeed, most of the aircraft crew studies were originally targeted at the effects of cosmic radiation, estimating cumulative radiation doses as exposure of interest. IARC explicitly assumes that the number of flights across several time zones, which is used as a proxy of frequency of circadian rhythm disruptions, correlates with the dose of cosmic radiation. Therefore, according to IARC, the estimates of cancer risk in cumulative radiation dose categories could also be interpreted to roughly reflect the frequency of circadian rhythm disruptions. This assumption, however, disregards that daytime flights in the north-south direction, thus along one meridian, would contribute to the radiation dose but per definition not lead to "circadian disruption".

The prostate cancer incidence in aircraft crews has been found elevated for pilots, but not for cabin crew, in several of the older studies. This excess risk has decreased over time and is, according to IARC, probably attributable to the use of prostate specific antigen (PSA) testing, which was common in pilots much earlier than in the general population. The two largest and most recent studies available in this category have found no elevated risks for prostate cancer mortality (20, 21). Only two reports on prostate cancer risks from other shift-working populations have been considered by IARC. In one study, a relative risk (RR) of 2.3 based on three cases was seen in persons working in fixed night shifts, while a RR of 3.0 (confidence interval (CI) 1.2 to 7.7; seven cases) resulted for rotating shift workers (22). The other study found an odds ratio (OR) of 1.19 (CI 1.0 to 1.42) for persons who "normally worked full-time rotating" shift, but it did not explain what "normally" meant (23). Contrary to IARC's reading of the paper there was no apparent trend with cumulative shift exposure. A third study did not enter into this comparison, which reported standardised incidence ratios close to unity for persons who worked in occupations with >40 % shift workers (6).

The evidence found by IARC for other cancers is even weaker and will not be discussed in detail in this

article. The picture gained so far, however, provokes the question whether there was indeed enough evidence for the carcinogenicity of shift work at the time of the IARC assessment to warrant a classification of this link as "probable". We may also ask whether this ruling, if warranted, should apply to all cancers or only to female breast cancer.

STUDIES SINCE THE IARC ASSESSMENT

We carried out a PubMed literature search using the search term "shift work OR night work OR circadian disruption AND cancer" for the period between 2007 and the end of 2011. This search yielded 363 hits, which were then restricted to ten original epidemiologic studies in humans; excluding reviews, studies targeting exposures that may include but go beyond shift work (e.g., light at night), and studies examining surrogates for effects (e.g., cancer biomarkers) (Table 2). One additional study, which was presented at the International EPICOH and MEDICHEM Meeting in Taiwan but has not been published to date, is further mentioned as personal communication.

Since 2007, six new studies have emerged which can shed more light on the possible link between shift work and female breast cancer. One study in a population-based Chinese cohort found a hazard ratio (HR) of 1.0 (CI 0.9 to 1.2) for ever working night shifts on the basis of a job exposure matrix; the HR was 0.9 (CI 0.7 to 1.1) on the basis of self-reported history of night shift work (24). In 2010, data from a nested case-control study in a different cohort consisting of 267,000 Chinese textile workers were presented for the first time in Taiwan. The RR for

Table 1 *Heterogeneity in exposure metrics and thresholds in female breast cancer studies (non-aircraft) quoted in the IARC assessment; *RR/OR = relative risk or odds ratio, as applicable; CI = confidence interval*

Study type	Population	Risk estimate (OR/RR; CI)*	Exposure to shift work	Source (ref number)
Cohort	Nurses, NHS (n=121,701)	1.36 (1.0 to 1.78)	≥30 years	Schernhammer et al. 2001 (4)
Cohort	Nurses, NHS II (n=116,087)	1.79 (1.06 to 3.01)	≥20 years	Schernhammer et al. 2006 (5)
Cohort	General population (n=1,148,661)	0.97 (0.67 to 1.40)	occupation with >40 % shift workers	Schwartzbaum et al. 2007 (6)
Nested case-control	Radio and telegraph operators, 50 cases, 4-7 matched controls	0.9 (0.3 to 2.9) 4.3 (0.7 to 26.0)	age <50 and shift work >3.1 years age ≥50 and shift work >3.1 years	Tynes et al. 1996 (7)
Case-control	General population, 7035 cases, one matched control per case	1.5 (1.2 to 1.7)	≥0.5 year in ≥1 trade in which ≥60 % of the female responders had night time schedules	Hansen 2001 (8)
Nested case-control	Nurses, 537 cases, 4 matched controls per case	1.3 (0.8 to 2.0) 2.2 (1.1 to 4.5)	15 to 29 years ≥30 years	Lie et al. 2006 (9)
Case-control	General population, 813 cases, 792 age matched controls	1.4 (1.0 to 2.0)	ever night shift (at least 3 nights per week)	Davis et al. 2001 (10)
Case-control	General population, 576 cases, 585 age matched controls	0.55 (0.3 to 0.9) 1.2 (0.9 to 1.6)	any overnight shift evening shift only	O'Leary et al. 2006 (11)

Table 2 *Studies on shift work and cancer, published after the IARC assessment; *RR/OR/HR = relative risk, odds ratio or hazard ratio, as applicable; CI = confidence interval*

Study type and cancer of interest	Population	Risk estimate (OR/RR/HR; CI)*	Exposure metric	Source (ref number)
Cohort Female breast	General population, Shanghai Women's Health Study, (n=73,049)	1.0 (0.9 to 1.2) 0.9 (0.7 to 1.1)	ever night shift (job exposure matrix) ever night shift (self-report)	Pronk et al. 2010 (24)
Case-control Female breast	General population, 857 cases, 892 controls	0.98 (0.74 to 1.29) 1.01 (0.68 to 1.50) 0.91 (0.38 to 2.18) 2.49 (0.87 to 7.18)	ever shift work ever night work 10 to 19 years night ≥20 years night	Pesch et al. 2010 (25)
Case-control Female breast	General population, 1230 cases, 1315 controls	1.4 (0.9 to 2.1) 2.4 (0.9 to 6.0) 1.5 (0.9 to 2.6)	employed >10 years as nurse textile workers tailors/dressmakers	Villeneuve et al. 2011 (26)
Nested case-control Female breast	Danish nurses, 310 cases, 4 age matched controls per case	0.9 (0.4 to 1.9) 1.8 (1.2 to 2.8) 2.9 (1.1 to 8.0)	ever evening shift, never night ever after midnight rotating shift, never permanent night ever permanent night in addition to rotating night shifts	Hansen and Stevens 2011 (27)
Nested case-control Female breast	Norwegian nurses, 699 cases, 895 frequency matched controls	1.1 (0.8 to 1.6) 1.2 (0.8 to 1.7) 1.8 (1.1 to 2.8)	worked ≥5 years with ≥3 consecutive night shifts worked <5 years with ≥6 consecutive night shifts worked ≥5 years with ≥6 consecutive night shifts	Lie et al. 2011 (28)
Cohort Prostate	4995 male industry workers, age 49 to 65 years (4168 daytime workers, 827 shift workers, 4 exposed cases)	1.79 (0.57 to 5.68)	three-shift work for >80 % of career	Kubo et al. 2011 (29)
Cohort Prostate	General population (15 million, 339,973 cases)	All risks for occupations with shift work around unity	Occupation with high probability for night work	Pukkala et al. 2009 (30)
Cohort Ovarian	Nurses, NHS I+II (n=181,548), 718 cases	1.28 (0.84 to 1.94) 0.80 (0.51 to 1.23)	15 to 19 years rotating night shift ≥20 years rotating night shift	Poole et al. 2011 (31)
Cohort Skin melanoma	Nurses, NHS I (n=68,336), 10,799 cases	0.80 (0.51 to 1.23) skin cancer 0.56 (0.36 to 0.87) melanoma	>10 years rotating shift	Schernhammer et al. 2011 (32)
Cohort Non-Hodgkin's lymphoma	General population (n=1,669,272), 6,307 NHL cases	1.10 (1.03 to 1.19)	Occupation with high probability for night work	Lahti et al. 2008 (33)

having worked shifts for 1 to <10 years, 10 to <20 years, and 20+ years compared with less than 1 year were 0.99, 1.0, and 0.92, respectively (W. Li, personal communication). In a re-analysis of case-control data originally gathered for a different set of risk factors, shift work (ever vs. never) had an OR for female breast cancer of 0.98 (CI 0.74 to 1.29); night work (ever vs. never) was associated with an OR of 1.01 (CI 0.68 to 1.50); there were non-significantly reduced risk estimates for exposure metrics below the median, and non-significantly increased risks above the median. The OR was 2.49 (CI 0.87 to 7.18) for more than 20 years of night shift work, while all other risk estimates were below unity (25). Surprisingly, the authors of this study concluded that their findings were "in line with the IARC classification." In a French case-control study on occupation as a risk factor for breast cancer, an OR of 1.4 (CI 0.9 to 2.1) emerged for women employed for more than 10 years as nurses. An overall OR of 2.4 (CI 0.9 to 6.0) was reported in textile workers and 1.5 (CI 0.9 to 2.6) in tailors/dressmakers, with no information available on working time schedules of these occupational groups (26). In a nested case-control study from a cohort of Danish nurses, significantly increased ORs ranging between 1.8 and 2.9 were found when work after midnight was compared with permanent day work (27). There was no apparent effect of evening work, if night work was excluded. An interesting new aspect was added by the re-analysis of data from a Norwegian case-control study (9, 28). Here, a significantly increased OR of 1.8 (CI 1.1 to 2.8) was seen in nurses who worked ≥5 years with ≥6 consecutive night shifts.

Two new studies have emerged regarding prostate cancer. An OR of 1.79 (CI 0.57 to 5.68), based on only four exposed cases, was seen in persons who had performed three-shift work for >80 % of their career, if compared to persons who had never worked shifts (29). On the other hand, no indication of an association with occupation was seen among 339,973 prostate cancer cases in a cohort of 15 million people aged 30 to 64 years in the 1960, 1970, 1980/1981 and/or 1990 censuses in Denmark, Finland, Iceland, Norway and Sweden (30).

Little new information has emerged for other cancer types. In one study, the HR for ovarian cancer was 1.28 (CI 0.84 to 1.94) in women who performed 15 to 19 years of rotating night shifts, and 0.80 (CI 0.51 to 1.23) for those with more than 20 years of shift work (31). A 14 % decreased risk of skin cancer, and 44 % decreased risk of melanoma, was seen after more than 10 years of rotating night shifts (32). The RR for non-Hodgkin's lymphoma was 1.10 (CI 1.03 to 1.19) for men who worked night shifts, and it increased to 1.28 (CI 1.03 to 1.59) when a lag period of 10 years was applied (33).

CONSEQUENCES FOR SHIFT WORKERS IN INDUSTRY - EXPERIENCE FROM A LARGE CHEMICAL COMPANY

While we agree with the conclusion drawn by Wang et al. (34) in their in-depth review that "heterogeneity of study exposures and outcomes and emphasis on positive but non-significant results make it difficult to draw general conclusions" from the existing literature on shift work and cancer, this lack of evidence should not lead to complacency in the persons who are responsible for workers' health. Recommendations for measures to counteract expected negative effects of night work are more often "eminence-based" than "evidence-based" (35). These recommendations include a selection of "shift tolerant" individuals, favouring of forward rotating shift schedules (morning - afternoon - night) over backward rotation (night - afternoon - day), avoidance of multiple night-shifts in a row, interventions through bright light or medication, physical exercise, and others.

Given that shift work is simply unavoidable in many occupations and industries, it is the duty of occupational physicians and scientists to examine the potential risks associated with this kind of work organisation. Health risks, if any, have to be minimised as far as possible and, where they can not be avoided, means of intervention and - if necessary - compensation have to be discussed. To this end we performed studies in more than 17.000 shift and 13.000 day workers at a major chemical site in Germany. We compared the acute and chronic illness experience, the accident rates, and the overall mortality across these groups of workers with the surprising result of generally more favourable outcomes for shift workers, after adjusting for smoking habits and other known relevant confounders (36, 37). Even the overall cancer incidence was reduced in shifts if compared to day workers. It has to be emphasised, however, that owing to German data protection legislation our database is weak regarding cancer incidence, and our conclusions regarding the question of carcinogenicity of shift work in our workforce are preliminary. There are several

possible explanations for the unexpected lack of adverse health effects of shift work in this study population. First, the shift system in place never requires more than one night shift in a row. Second, it is forward rotating, with night work always followed by a resting period of 24 (old system) or 48 hours (new system). With regard to the IARC concept of "circadian disruption", we hypothesise that desynchronisation of circadian biological rhythms does not occur to a sizable degree under these circumstances. This assumption can further be supported by the observation that workers in both shift systems did not complain about subjective health impairment more than day workers with the same socio-economic background (38). Whether health promotion programs for workers result in long-term health benefits is equivocal (39, 40), but it may reasonably be assumed provided such programs are not only offered on a one-time basis. We were indeed able to demonstrate that shift workers in our studied populations were more often participating in such programs than day workers, and participation in health promotion activities was associated with reduced overall mortality, if compared to non-participation (41). However this reduced mortality was not apparently triggered by reduced cancer incidence in participants (RR 1.07; CI 0.84 to 1.36).

CONCLUSION

Based on the literature available, it can not be confidently ruled out that shift work including night work may, possibly depending on the way how it is organised, increase the risk for some cancers in those who perform it. However, at this point in time there is no reason to believe that shift-workers in general face an increased cancer risk. In any case, shift schedules can probably be organised in ways that minimise the associated health risks, and the risks may be further reduced through the implementation of structured and sustained health promotion programs specifically tailored to the needs of shift workers. The recommendation to use fast forward rotating shift schedules with no more than one or two subsequent night shifts can be supported on the basis of our experience.

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Sažetak

RAD U SMJENAMA I RAK - ZNANSTVENE SPOZNAJE I PRAKTIČNE POSLJEDICE

Stručna radna skupina, koju je okupio Program monografija Međunarodne agencije za istraživanje raka (eng. *International Agency for Research on Cancer*, krat. IARC), 2007. godine zaključila je da je rad u smjenama, koji uključuje prekid cirkadijurnoga ritma, najvjerojatnije kancerogen za ljude (skupina 2A). Procijenili smo epidemiološku osnovu takvoga zaključka i usredotočili se na rak dojke i rak prostate između ostalih malignih bolesti. Nadalje, razmatrali smo praktične posljedice koje rad u smjenama ima na radnike u kemijskoj kompaniji BASF u okvirima novih spoznaja na tom području.

Istražili smo literaturu, uključujući i epidemiološka istraživanja studije koje citira IARC kao i noviju literaturu o povezanosti rada u smjenama i raku.

Od zaključka IARC-a nastalo je jedanaest novih istraživanja, a deset ih je već objavljeno. Njihovi rezultati ipak ne dovode do konačnoga i jednoznačnoga zaključka. Heterogenost mjerenja izloženosti i ishoda istraživanja i naglasak na pozitivne, ali ne uvijek i značajne rezultate, otežavaju postavljanje općih zaključaka. Jednako tako u nekoliko nedavno objavljenih recenzija i komentara ne iznose se jednoznačni rezultati. Objavljeni znanstveno utemeljeni dokazi samo upućuju, ali ne dovode u očiglednu vezu noćni rad i rak dojke. Nadalje, ograničeni su i nedosljedni za malignome na drugim lokacijama u tijelu, kao i za sve malignome zajedno.

U ovom trenutku nije moguće odbaciti hipotezu da smjenski rad (uključujući noćni rad) može povećati rizik nastanka određenih malignih bolesti. Međutim, raspored smjena se može organizirati na način da se opasnosti za zdravlje svedu na najmanju moguću mjeru. Rizici se također mogu dodatno smanjiti provedbom strukturiranih programa promicanja održivoga zdravlja koji bi bili posebno osmišljeni prema potrebama radnika.

KLJUČNE RIJEČI: *noćni rad, prekid cirkadijurnog ritma, rak dojke, rak prostate*

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